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L29 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2006:540258 HCAPLUS
ED Entered STN: 08 Jun 2006
TI Stimulation of the soluble **guanylyl cyclase** **mutant** activity as reveled by Resonance Raman spectroscopy
AU Czarnecki, Kazimierz; **Martin, Emil**; Kincaid, James
CS Department of Chemistry, Marquette University, Milwaukee, WI, 53233, USA
SO Abstracts, 37th Great Lakes Regional Meeting of the American Chemical Society, Milwaukee, WI, United States, May 31-June 2 (2006), GLRM-054
Publisher: American Chemical Society, Washington, D. C.
CODEN: 69ICX4
DT Conference; Meeting Abstract
LA English
AB Soluble **guanylyl cyclase** (sGC) plays key roles in many physiol. processes in the central nervous system. It is a heme-enzyme, which acts as a NO receptor, negotiating the conversion of guanosine triphosphate (GTP) into secondary messenger, guanosine 3',5'-cyclic monophosphate (cGMP) following binding of NO to the prosthetic heme group. Recent studies have shown that, in the presence of certain allosteric modulators, sGC can be activated by CO. While many heme proteins capable of binding NO and CO can also bind O2, sGC effectively discriminates against dioxygen, somehow. Lately, the study of the structure and function of various site-directed **mutants** of this protein have been undertaken in attempts to understand its ability to regulate binding of different diat. substrates. Given the well documented power of resonance Raman (RR) spectroscopy to reveal active site structural detail for heme protein adducts, it is not surprising that this technique is being effectively applied to this problem. The present report focuses on the characterization of active site structural features of the native and **mutant** sGC proteins from human lung. The specific **mutant** being studied involves replacement of an active site isoleucine with tyrosine, a potential H-bond donor residue (i.e., sGC I145Y); in addition to the holo-enzyme of the **mutant**, a truncated form of the

mutant, reportedly capable of binding dioxygen, is also being studied. In addition to probing the active site structure in the resting state, efforts are made to document RR spectral changes associated with binding of the different diatomics in the absence and presence of natural substrates and products, as well various synthetic allosteric effectors.

L29 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:913015 HCAPLUS
DN 142:34238
ED Entered STN: 01 Nov 2004
TI CCTη, a Novel Soluble **Guanylyl Cyclase**-interacting Protein
AU Hanafy, Khalid A.; **Martin, Emil; Murad, Ferid**
CS Department of Integrative Biology and Pharmacology, Institute of Molecular Medicine, University of Texas Medical School, Houston, TX, 77030, USA
SO Journal of Biological Chemistry (2004), 279(45), 46946-46953
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 6-3 (General Biochemistry)
Section cross-reference(s): 7
AB Nitric oxide (NO) transduces most of its biol. effects through activation of the heterodimeric enzyme, soluble **guanylyl cyclase** (sGC). Activation of sGC results in the production of cGMP from GTP. In this paper, we demonstrate a novel protein interaction between CCT (chaperonin containing t-complex polypeptide) subunit η and the α1β1 isoform of sGC. CCTη was found to interact with the β1 subunit of sGC via a yeast-two-hybrid screen. This interaction was then confirmed in vitro with a co-immunopptn. from mouse brain. The interaction between these two proteins was further supported by a co-localization of the proteins within rat brain. Using the yeast two-hybrid system, CCTη was found to bind to the N-terminal portion of sGC. In vitro assays with purified CCTη and Sf9 lysate expressing sGC resulted in a 30-50% inhibition of diethylamine diazeniumdiolate-NO-stimulated sGC activity. The same assays were then performed using BAY41-2272, an NO-independent allosteric sGC activator, and CCTη had no effect on this activity. Furthermore, CCTη had no effect on basal or sodium nitroprusside-stimulated α **.beta.Cys-105** sGC, a constitutively active **mutant** that only lacks the heme group. The N-terminal 94 amino acids of CCTη seem to be critical for the mediation of this inhibition. Lastly, a 45% inhibition of sGC activity by CCTη was seen in vivo in BE2 cells stably transfected with CCTη and treated with sodium nitroprusside. These data suggest that CCTη binds to sGC and, in cooperation with some other factor, inhibits its activity by modifying the binding of NO to the heme group or the subsequent conformational changes.
ST CCTeta interaction **guanylyl cyclase** brain conformation
IT Proteins
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(CCTη (chaperonin containing t-complex polypeptide) subunit η; N-terminal of chaperonin containing t-complex polypeptide subunit η interacts with soluble **guanylyl cyclase** in rat brain)
IT Allosterism
Conformational transition
(CCTη in cooperation with sodium nitroprusside can mediate NO-dependent inhibition of soluble **guanylyl cyclase** through conformational transition)
IT Molecular association

(CCTη-soluble **guanylyl cyclase**; N-terminal of chaperonin containing t-complex polypeptide subunit η interacts with soluble **guanylyl cyclase** in rat brain)

IT Brain
(N-terminal of chaperonin containing t-complex polypeptide subunit η interacts with soluble **guanylyl cyclase** in rat brain)

IT Protein motifs
(N-terminal; N-terminal of chaperonin containing t-complex polypeptide subunit η interacts with soluble **guanylyl cyclase** in rat brain)

IT Proteins
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(β1 subunit; N-terminal of chaperonin containing t-complex polypeptide subunit η interacts with soluble **guanylyl cyclase** in rat brain)

IT 10102-43-9, Nitric oxide, biological studies 14402-89-2, Sodium nitroprusside 14875-96-8, Heme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CCTη in cooperation with sodium nitroprusside can mediate NO-dependent inhibition of soluble **guanylyl cyclase** through conformational transition)

IT **9054-75-5, Guanylyl cyclase**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(N-terminal of chaperonin containing t-complex polypeptide subunit η interacts with soluble **guanylyl cyclase** in rat brain)

RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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IT **9054-75-5, Guanylyl cyclase**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(N-terminal of chaperonin containing t-complex polypeptide subunit η interacts with soluble **guanylyl cyclase** in rat brain)

RN 9054-75-5 HCAPLUS
CN Cyclase, guanylate (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L29 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:857321 HCAPLUS
DN 141:307614

ED Entered STN: 18 Oct 2004
TI Treatment or prevention of **cGMP**-dependent pathophysiology with a **mutant** variant of soluble **guanylyl cyclase** (sGC)
IN **Martin, Emil; Murad, Ferid**
PA The Board of Regents of the University of Texas System, USA
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K
CC 1-12 (Pharmacology)
Section cross-reference(s): 7

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004087046	A2	20041014	WO 2004-US3853	20040211 <--
	WO 2004087046	A3	20050127		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2004235079	A1	20041125	US 2004-777008	20040211 <--
	EP 1592787	A2	20051109	EP 2004-749320	20040211 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
PRAI	US 2003-446427P	P	20030211 <--		
	WO 2004-US3853	W	20040211 <--		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004087046	ICM	A61K
	IPCI	A61K [ICM,7]
	IPCR	A61K [I,S]; C12N0009-12 [I,A]; C12N0009-12 [I,C*]; C12N0015-09 [I,A]; C12N0015-09 [I,C*]; C12Q0001-42 [I,A]; C12Q0001-42 [I,C*]; C12Q0001-48 [I,A]; C12Q0001-48 [I,C*]
US 2004235079	IPCI	C12Q0001-42 [ICM,7]
	IPCR	C12Q0001-42 [I,A]; C12Q0001-42 [I,C*]
	NCL	435/021.000
EP 1592787	IPCI	C12N0009-12 [ICM,7]; C12N0015-09 [ICS,7]; C12Q0001-42 [ICS,7]; C12Q0001-48 [ICS,7]
	IPCR	A61K [I,S]; C12N0009-12 [I,A]; C12N0009-12 [I,C*]; C12N0015-09 [I,A]; C12N0015-09 [I,C*]; C12Q0001-42 [I,A]; C12Q0001-42 [I,C*]; C12Q0001-48 [I,A]; C12Q0001-48 [I,C*]

AB Methods of using a heme-deficient **mutant** sGC with a substituted His105 residue, which has a high basal specific activity and displays properties similar to NO-stimulated wild type sGC, are disclosed. Preferred embodiments aid in the prevention and treatment of cyclic GMP-dependent pathphysiologies, and are useful in the development of drugs that inhibit or activate sGC. Certain embodiments provide a method of treating angina and other chronic heart diseases comprising delivery of a constitutively active α .**beta.Cys105**

mutant gene or enzyme to an in vivo cell.

ST cyclic GMP disease treatment **mutant** sol **guanylyl cyclase**; angina treatment **mutant** sol **guanylyl cyclase**; chronic heart disease treatment **mutant** sol **guanylyl cyclase**

IT Heart, disease
(angina pectoris; soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT Antiarteriosclerotics
(antiatherosclerotics; soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT Heart, disease
Hypertension
(chronic; soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT Heart, disease
(failure; soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT Heart, disease
(infarction; soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT Neoplasm
(metastasis; soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT Penis
(penile dysfunction; soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT Shock (circulatory collapse)
(septic; soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT Allosterism
Anticoagulants
Antihypertensives
Antitumor agents
Atherosclerosis
Cardiovascular agents
Cardiovascular system, disease
Chemical library
Drug screening
Michaelis constant
Mutagenesis
Neoplasm
Thrombosis
(soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT Vein
(transplant; soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT Transplant and Transplantation
(vein; soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT Crystals
(α β **Cys105 mutant** soluble **guanylyl cyclase**; soluble **guanylyl cyclase mutant** for treatment or prevention of **cGMP**-dependent pathophysiol.)

IT **86-01-1**, **GTP 7665-99-8**, Cyclic GMP

10102-43-9, Nitric oxide, biological studies 14875-96-8, Heme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(soluble **guanylyl cyclase mutant** for
treatment or prevention of **cGMP**-dependent pathophysiol.)

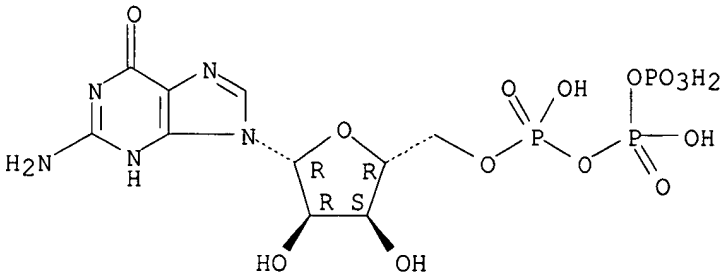
IT **9054-75-5, Guanylyl cyclase**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(soluble **guanylyl cyclase mutant** for
treatment or prevention of **cGMP**-dependent pathophysiol.)

IT 51-85-4, Cystamine 70-18-8, GSH, biological studies 506-32-1, Arachidonic acid 553-12-8, Protoporphyrin IX 3483-12-3, DTT 14402-89-2, Sodium nitroprusside 16009-13-5, Hemin 170632-47-0, YC-1
RL: PAC (Pharmacological activity); BIOL (Biological study)
(soluble **guanylyl cyclase mutant** for
treatment or prevention of **cGMP**-dependent pathophysiol.)

IT **86-01-1, GTP 7665-99-8,** Cyclic GMP
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(soluble **guanylyl cyclase mutant** for
treatment or prevention of **cGMP**-dependent pathophysiol.)

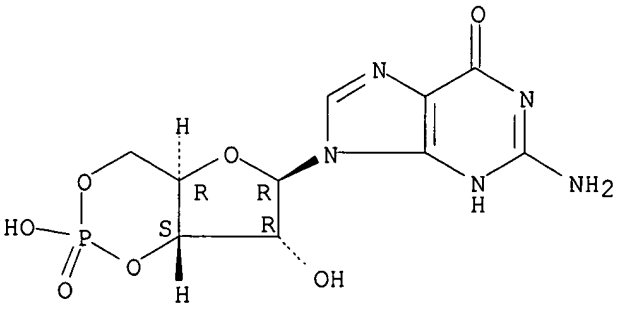
RN 86-01-1 HCAPLUS
CN Guanosine 5'-(tetrahydrogen triphosphate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 7665-99-8 HCAPLUS
CN Guanosine, cyclic 3',5'-(hydrogen phosphate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9054-75-5, Guanylyl cyclase**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(soluble **guanylyl cyclase mutant** for
treatment or prevention of **cGMP**-dependent pathophysiol.)

RN 9054-75-5 HCAPLUS

CN Cyclase, guanylate (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L29 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2003:638740 HCAPLUS
DN 139:272820
ED Entered STN: 17 Aug 2003
TI A constitutively activated **mutant** of human soluble **guanylyl cyclase** (sGC): Implication for the mechanism of sGC activation
AU **Martin, Emil**; Sharina, Iraida; Kots, Alexander; **Murad, Ferid**
CS Department of Integrative Biology and Pharmacology and Institute of Molecular Medicine, University of Texas Health Science Center, Houston, TX, 77030, USA
SO Proceedings of the National Academy of Sciences of the United States of America (2003), 100(16), 9208-9213
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 7-3 (Enzymes)
AB Heterodimeric αβ soluble **guanylyl cyclase** (sGC) is a recognized receptor for nitric oxide (NO) and mediates many of its physiol. functions. Although it has been clear that the heme moiety coordinated by His-105 of the β subunit is crucial for mediating the activation of the enzyme by NO, it is not understood whether the heme moiety plays any role in the function of the enzyme in the absence of NO. Here we analyze the effects of biochem. and genetic removal of heme and its reconstitution on the activity of the enzyme. Detergent-induced loss of heme from the wild-type αβ enzyme resulted in several-fold activation of the enzyme. This activation was inhibited after hemin reconstitution. A heme-deficient **mutant** α . **beta.Cys-105** with Cys substituted for His-105 was constitutively active with specific activity approaching the activity of the wild-type enzyme activated by NO. However, reconstitution of **mutant** enzyme with heme and/or DTT treatment significantly inhibited the enzyme. **Mutant** enzyme reconstituted with ferrous heme was activated by NO and CO alone and showed additive effects between gaseous effectors and the allosteric activator 5-cyclopropyl-2-[1-(2-fluoro-benzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-yrimidin-4-ylamine. We propose that the heme moiety through its coordination with His-105 of the β subunit acts as an endogenous inhibitor of sGC. Disruption of the heme-coordinating bond induced by binding of NO releases the restrictions imposed by this bond and allows the formation of an optimally organized catalytic center in the heterodimer.
ST **guanylyl cyclase** human nitric oxide hemin heme iron
IT Allosterism
Human
(heme prosthetic group of soluble **guanylyl cyclase** maintains enzyme basal state with regulatory domain in inhibited restricted conformation through coordination with axial His105 residue)
IT Conformation
(protein; heme prosthetic group of soluble **guanylyl cyclase** maintains enzyme basal state with regulatory domain in inhibited restricted conformation through coordination with axial His105 residue)
IT Protein motifs
(regulatory domain; heme prosthetic group of soluble **guanylyl**

cyclase maintains enzyme basal state with regulatory domain in inhibited restricted conformation through coordination with axial His105 residue)

IT 52-90-4, L-Cysteine, biological studies 71-00-1, L-Histidine, biological studies **86-01-1**, 5'-**GTP** 630-08-0, Carbon monoxide, biological studies 3483-12-3, Dithiothreitol 7439-89-6, Iron, biological studies 7439-95-4, Magnesium, biological studies **7665-99-8**, **CGMP** 10102-43-9, Nitric oxide, biological studies 14875-96-8, Heme 16009-13-5, Hemin 20074-52-6, biological studies 256376-24-6, BAY 41-2272
RL: BSU (Biological study, unclassified); BIOL (Biological study) (heme prosthetic group of soluble **guanylyl cyclase** maintains enzyme basal state with regulatory domain in inhibited restricted conformation through coordination with axial His105 residue)

IT **9054-75-5**, **Guanylyl cyclase**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (soluble; heme prosthetic group of soluble **guanylyl cyclase** maintains enzyme basal state with regulatory domain in inhibited restricted conformation through coordination with axial His105 residue)

RE.CNT 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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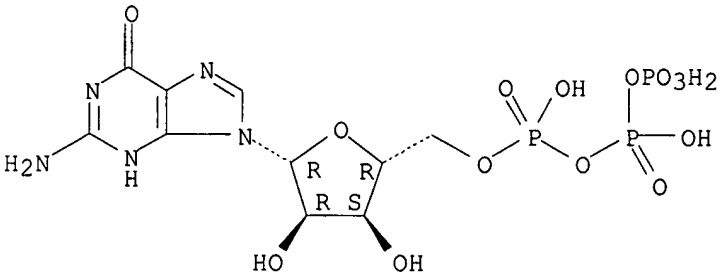
IT **86-01-1**, 5'-**GTP 7665-99-8, CGMP**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(heme prosthetic group of soluble **guanylyl cyclase** maintains enzyme basal state with regulatory domain in inhibited restricted conformation through coordination with axial His105 residue)

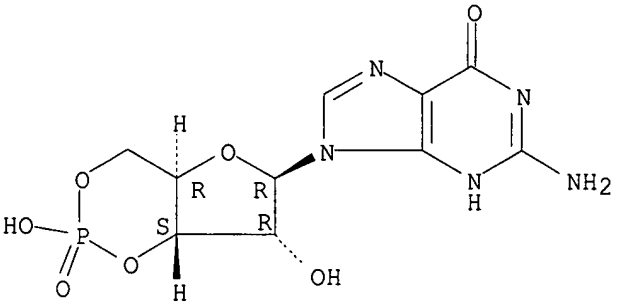
RN 86-01-1 HCAPLUS
CN Guanosine 5'-(tetrahydrogen triphosphate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 7665-99-8 HCAPLUS
CN Guanosine, cyclic 3',5'-(hydrogen phosphate) (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9054-75-5, Guanylyl cyclase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(soluble; heme prosthetic group of soluble **guanylyl cyclase** maintains enzyme basal state with regulatory domain in inhibited restricted conformation through coordination with axial His105 residue)

RN 9054-75-5 HCAPLUS
CN Cyclase, guanylate (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L29 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2006 ACS on STN
AN 2001:858299 HCAPLUS
DN 136:81841
ED Entered STN: 28 Nov 2001
TI YC-1 activation of human soluble **guanylyl cyclase** has both heme-dependent and heme-independent components
AU **Martin, Emil**; Lee, Yu-Chen; **Murad, Ferid**

CS Department of Integrative Biology and Pharmacology, Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX, 77030, USA
SO Proceedings of the National Academy of Sciences of the United States of America (2001), 98(23), 12938-12942
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 7-3 (Enzymes)
AB YC-1 [3-(5'-hydroxymethyl-2'furyl)-1-benzyl indazole] is an allosteric activator of soluble **guanylyl cyclase** (sGC). YC-1 increases the catalytic rate of the enzyme and sensitizes the enzyme toward its gaseous activators nitric oxide or carbon monoxide. In other studies the administration of YC-1 to exptl. animals resulted in the inhibition of the platelet-rich thrombosis and a decrease of the mean arterial pressure, which correlated with increased cGMP levels. However, details of YC-1 interaction with sGC and enzyme activation are incomplete. Although evidence in the literature indicates that YC-1 activation of sGC is strictly heme-dependent, this report presents evidence for both heme-dependent and heme-independent activation of sGC by YC-1. The oxidation of the sGC heme by 1H-(1,2,4)oxadiazole(4,3-a)quinoxalin-1-one completely inhibited the response to NO, but only partially attenuated activation by YC-1. We also observed activation by YC-1 of a **mutant** sGC, which lacks heme. These findings indicate that YC-1 activation of sGC can occur independently of heme, but that activation is substantially increased when the heme moiety is present in the enzyme.
ST YC1 activation **guanylyl cyclase**; hydroxymethylfurylbenzyl indazole **guanylyl cyclase** activation
IT Human
(YC-1 activation of human soluble **guanylyl cyclase** has both heme-dependent and heme-independent components)
IT **9054-75-5, Guanylyl cyclase** 14875-96-8, Heme 41443-28-1, ODQ 170632-47-0, YC-1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(YC-1 activation of human soluble **guanylyl cyclase** has both heme-dependent and heme-independent components)
RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Abrams, J; Am J Cardiol 1996, V77, P31C HCAPLUS
(2) Denninger, J; Biochemistry 2000, V39, P4191 HCAPLUS
(3) Denninger, J; Biochim Biophys Acta 1999, V1411, P334 HCAPLUS
(4) Feelisch, M; Mol Pharmacol 1999, V56, P243 HCAPLUS
(5) Friebe, A; EMBO J 1996, V15, P6863 HCAPLUS
(6) Friebe, A; Mol Pharmacol 1998, V53, P123 HCAPLUS
(7) Friebe, A; Mol Pharmacol 1998, V54, P962 HCAPLUS
(8) Garthwaite, J; Mol Pharmacol 1995, V48, P184 HCAPLUS
(9) Hoenicka, M; J Mol Med 1999, V77, P14 HCAPLUS
(10) Kharitonov, V; Biochemistry 1999, V38, P10699 HCAPLUS
(11) Lee, Y; Proc Natl Acad Sci USA 2000, V97, P10763 HCAPLUS
(12) Lee, Y; Proc Natl Acad Sci USA 2000, V97, P10763 HCAPLUS
(13) Martin, E; Semin Perinatol 2000, V24, P2 MEDLINE
(14) Mulsch, A; Br J Pharmacol 1997, V120, P681 MEDLINE
(15) Rothermund, L; Br J Pharmacol 2000, V130, P205 HCAPLUS
(16) Schrammel, A; Mol Pharmacol 1996, V50, P1 HCAPLUS
(17) Sharma, V; Biochem Biophys Res Commun 1999, V254, P188 HCAPLUS
(18) Stasch, J; Nature (London) 2001, V410, P212 HCAPLUS
(19) Stone, J; Biochemistry 1994, V33, P5636 HCAPLUS
(20) Teng, C; Eur J Pharmacol 1997, V320, P161 HCAPLUS

(21) Torfgard, K; Cardiovasc Drugs Ther 1994, V8, P701 MEDLINE
(22) Wedel, B; Proc Natl Acad Sci USA 1994, V91, P2592 HCAPLUS
(23) Zhao, Y; Biochemistry 1997, V36, P15959 HCAPLUS
(24) Zhao, Y; Biochemistry 2000, V39, P10848 HCAPLUS
IT **9054-75-5, Guanylyl cyclase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(YC-1 activation of human soluble **guanylyl cyclase** has both heme-dependent and heme-independent components)
RN 9054-75-5 HCAPLUS
CN Cyclase, guanylate (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> => fil reg
FILE 'REGISTRY' ENTERED AT 15:12:18 ON 13 JUL 2006

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 12 JUL 2006 HIGHEST RN 892389-74-1
DICTIONARY FILE UPDATES: 12 JUL 2006 HIGHEST RN 892389-74-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> L62 3 L61 AND (L6 OR L7 OR L8 OR L18 OR L19)

=> d ide can tot

L62 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2006 ACS on STN
RN **9054-75-5** REGISTRY
ED Entered STN: 16 Nov 1984
CN Cyclase, guanylate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 45: PN: WO2005016244 PAGE: 68 claimed sequence
CN E.C. 4.6.1.2
CN Guanyl cyclase
CN Guanylate cyclase
CN **Guanylyl cyclase**
CN ST enterotoxin receptors
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CIN, EMBASE, IPA, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5373 REFERENCES IN FILE CA (1907 TO DATE)
22 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5392 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 145:44253

REFERENCE 2: 145:43602

REFERENCE 3: 145:43574

REFERENCE 4: 145:43345

REFERENCE 5: 145:43296

REFERENCE 6: 145:40656

REFERENCE 7: 145:40609

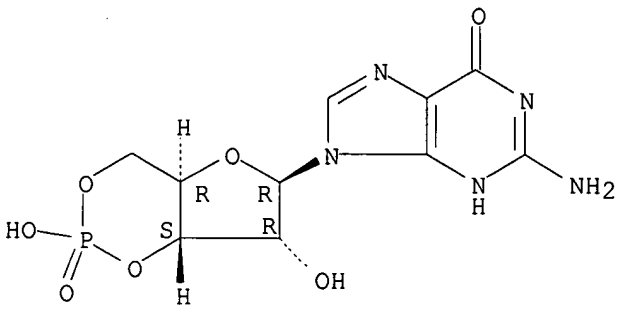
REFERENCE 8: 145:40323

REFERENCE 9: 145:24765

REFERENCE 10: 145:24720

L62 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2006 ACS on STN
RN **7665-99-8** REGISTRY
ED Entered STN: 16 Nov 1984
CN Guanosine, cyclic 3',5'-(hydrogen phosphate) (8CI, 9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4H-Furo[3,2-d]-1,3,2-dioxaphosphorin, guanosine deriv.
CN Guanosine 3',5'-phosphate (cyclic) (7CI)
OTHER NAMES:
CN 3',5'-Cyclic GMP
CN 3',5'-GMP
CN **cGMP**
CN Cyclic 3',5'-GMP
CN Cyclic 3',5'-guanylic acid
CN Cyclic GMP
CN Cyclic guanosine 3',5'-monophosphate
CN Cyclic guanosine monophosphate
CN Guanosine 3',5'-monophosphate
CN Guanosine 3',5'-phosphate
CN Guanosine cyclic 3',5'-monophosphate
CN Guanosine cyclic 3',5'-phosphate
FS STEREOSEARCH
DR 3545-77-5
MF C10 H12 N5 O7 P
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT, PIRA, PROMT, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

16334 REFERENCES IN FILE CA (1907 TO DATE)
75 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
16353 REFERENCES IN FILE CAPLUS (1907 TO DATE)
5 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 145:44367

REFERENCE 2: 145:44253

REFERENCE 3: 145:44108

REFERENCE 4: 145:44095

REFERENCE 5: 145:43602

REFERENCE 6: 145:43574

REFERENCE 7: 145:43508

REFERENCE 8: 145:43479

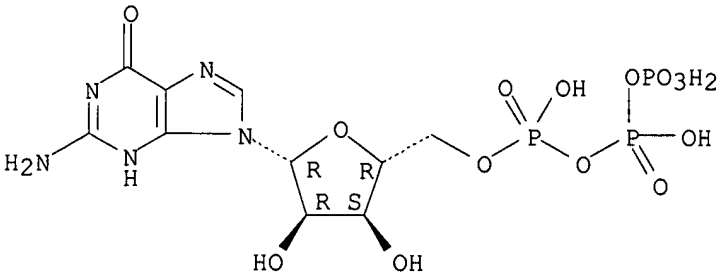
REFERENCE 9: 145:43477

REFERENCE 10: 145:43298

L62 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2006 ACS on STN
RN **86-01-1** REGISTRY
ED Entered STN: 16 Nov 1984
CN Guanosine 5'-(tetrahydrogen triphosphate) (8CI, 9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Guanosine triphosphate (6CI)
OTHER NAMES:
CN 5'-GTP
CN **GTP**
CN Guanosine 5'-triphosphate
CN Guanosine 5'-triphosphoric acid
CN Guanosine, mono(tetrahydrogen triphosphate) (ester)
FS STEREOSEARCH
DR 7482-81-7, 362-82-3
MF C10 H16 N5 O14 P3
CI COM
SR CA

LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMLIST, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, MSDS-OHS, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

13600 REFERENCES IN FILE CA (1907 TO DATE)
755 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
13605 REFERENCES IN FILE CAPLUS (1907 TO DATE)
117 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 145:44348

REFERENCE 2: 145:43300

REFERENCE 3: 145:42662

REFERENCE 4: 145:41705

REFERENCE 5: 145:33888

REFERENCE 6: 145:23718

REFERENCE 7: 145:23144

REFERENCE 8: 145:23078

REFERENCE 9: 145:22924

REFERENCE 10: 145:22920

=> fil medline
FILE 'MEDLINE' ENTERED AT 15:12:51 ON 13 JUL 2006

FILE LAST UPDATED: 12 JUL 2006 (20060712/UP). FILE COVERS 1950 TO DATE.

On December 11, 2005, the 2006 MeSH terms were loaded.

The MEDLINE reload for 2006 is now (26 Feb.) available. For details on the 2006 reload, enter HELP RLOAD at an arrow prompt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_med_data_changes.html
http://www.nlm.nih.gov/pubs/techbull/nd05/nd05_2006_MeSH.html

OLDMEDLINE is covered back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2006 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all 160

L60 ANSWER 1 OF 1 MEDLINE on STN
AN 2004573678 MEDLINE
DN PubMed ID: 15347653
TI CCTeta, a novel soluble **guanylyl cyclase**-interacting protein.
AU Hanafy Khalid A; Martin Emil; Murad Ferid
CS Department of Integrative Biology and Pharmacology and Institute of Molecular Medicine, University of Texas Medical School, Houston, Texas 77030, USA.
NC GM61731 (NIGMS)
HL64221 (NHLBI)
SO The Journal of biological chemistry, (2004 Nov 5) Vol. 279, No. 45, pp. 46946-53. Electronic Publication: 2004-08-30.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200412
ED Entered STN: 20 Nov 2004
Last Updated on STN: 29 Dec 2004
Entered Medline: 28 Dec 2004
AB Nitric oxide (NO) transduces most of its biological effects through activation of the heterodimeric enzyme, soluble **guanylyl cyclase** (sGC). Activation of sGC results in the production of cGMP from GTP. In this paper, we demonstrate a novel protein interaction between CCT (chaperonin containing t-complex polypeptide) subunit eta and the alphalbeta1 isoform of sGC. CCTeta was found to interact with the beta1 subunit of sGC via a yeast-two-hybrid screen. This interaction was then confirmed in vitro with a co-immunoprecipitation from mouse brain. The interaction between these two proteins was further supported by a co-localization of the proteins within rat brain. Using the yeast two-hybrid system, CCTeta was found to bind to the N-terminal portion of sGC. In vitro assays with purified CCTeta and Sf9 lysate expressing sGC resulted in a 30-50% inhibition of diethylamine diazeniumdiolate-NO-stimulated sGC activity. The same assays were then performed using BAY41-2272, an NO-independent allosteric sGC activator, and CCTeta had no effect on this activity. Furthermore, CCTeta had no effect on basal or sodium nitroprusside-stimulated alphabeta(**Cys-105**) sGC, a constitutively active mutant that only lacks the heme group. The N-terminal 94 amino acids of CCTeta seem to be critical for the mediation

of this inhibition. Lastly, a 45% inhibition of sGC activity by CCTeta was seen in vivo in BE2 cells stably transfected with CCTeta and treated with sodium nitroprusside. These data suggest that CCTeta binds to sGC and, in cooperation with some other factor, inhibits its activity by modifying the binding of NO to the heme group or the subsequent conformational changes.

CT Animals
Blotting, Western
Brain: ME, metabolism
Cell Line
*Chaperonins: CH, chemistry
*Chaperonins: ME, metabolism
Cloning, Molecular
Cyclic GMP: ME, metabolism
Dose-Response Relationship, Drug
Gene Deletion
Guanosine Triphosphate: ME, metabolism
***Guanylate Cyclase: ME, metabolism**
Hippocampus: ME, metabolism
Histidine: CH, chemistry
Immunohistochemistry
Immunoprecipitation
Insects
Mice
Mice, Inbred C57BL
Microscopy, Confocal
Mutation
*Nitric Oxide: ME, metabolism
Nitroprusside: PD, pharmacology
Protein Binding
Protein Conformation
Protein Isoforms
Protein Structure, Tertiary
Radioimmunoassay
Rats
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
Research Support, U.S. Gov't, P.H.S.
Tissue Distribution
Transfection
Two-Hybrid System Techniques
alpha-Galactosidase: ME, metabolism

RN 10102-43-9 (Nitric Oxide); 15078-28-1 (Nitroprusside); 71-00-1 (Histidine); 7665-99-8 (Cyclic GMP); 86-01-1 (Guanosine Triphosphate)

CN 0 (CCTeta protein, mouse); 0 (Chaperonins); 0 (Protein Isoforms); EC 3.2.1.22 (alpha-Galactosidase); **EC 4.6.1.2 (Guanylate Cyclase)**

=> fil biosis
FILE 'BIOSIS' ENTERED AT 15:13:12 ON 13 JUL 2006

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 12 July 2006 (20060712/ED)

=> d all tot l40

L40 ANSWER 1 OF 3 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2005:106136 BIOSIS
DN PREV200500104126
TI CCTeta, a novel soluble **guanylyl cyclase**-interacting protein.
AU Hanafy, Khalid A.; **Martin, Emil; Murad, Ferid** [Reprint Author]
CS Houston Sch MedDept Integrat Biol and Pharmacol, Univ Texas, 6431 Fannin, Houston, TX, 77030, USA
ferid.murad@uth.tmc.edu
SO Journal of Biological Chemistry, (November 5 2004) Vol. 279, No. 45, pp. 46946-46953. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DT Article
LA English
ED Entered STN: 16 Mar 2005
Last Updated on STN: 16 Mar 2005
AB Nitric oxide (NO) transduces most of its biological effects through activation of the heterodimeric enzyme, soluble **guanylyl cyclase** (sGC). Activation of sGC results in the production of cGMP from GTP. In this paper, we demonstrate a novel protein interaction between CCT (chaperonin containing t-complex polypeptide) subunit eta and the alpha1beta1 isoform of sGC. CCTeta was found to interact with the beta1 subunit of sGC via a yeast-two-hybrid screen. This interaction was then confirmed in vitro with a co-immunoprecipitation from mouse brain. The interaction between these two proteins was further supported by a co-localization of the proteins within rat brain. Using the yeast two-hybrid system, CCTeta was found to bind to the N-terminal portion of sGC. In vitro assays with purified CCTeta and Sf9 lysate expressing sGC resulted in a 30-50% inhibition of diethylamine diazeniumdiolate-NO-stimulated sGC activity. The same assays were then performed using BAY41-2272, an NO-independent allosteric sGC activator, and CCTeta had no effect on this activity. Furthermore, CCTeta had no effect on basal or sodium nitroprusside-stimulated alphabetaCys-105 sGC, a constitutively active **mutant** that only lacks the heme group. The N-terminal 94 amino acids of CCTeta seem to be critical for the mediation of this inhibition. Lastly, a 45% inhibition of sGC activity by CCTeta was seen in vivo in BE2 cells stably transfected with CCTeta and treated with sodium nitroprusside. These data suggest that CCTeta binds to sGC and, in cooperation with some other factor, inhibits its activity by modifying the binding of NO to the heme group or the subsequent conformational changes.
CC Genetics - General 03502
Genetics - Plant 03504
Genetics - Animal 03506
Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Enzymes - General and comparative studies: coenzymes 10802
Nervous system - Physiology and biochemistry 20504
IT Major Concepts
Molecular Genetics (Biochemistry and Molecular Biophysics); Nervous System (Neural Coordination)
IT Parts, Structures, & Systems of Organisms
brain: nervous system
IT Chemicals & Biochemicals
BAY41-2272: nitric oxide-soluble **guanylyl cyclase** activator; GTP; Sf9 lysate; cGMP [cyclic GMP]; chaperonin containing t-complex polypeptide: subunit eta; diethylamine diazeniumdiolate; nitric oxide; nitric-oxide synthase [EC 1.14.13.39]; sodium

nitroprusside; soluble **guanylyl cyclase** [**EC 4.6.1.2**]: N- terminal portion, alpha-1-beta-1 iosform, beta-1 subunit, heterodimeric enzyme
IT Methods & Equipment
co-immunoprecipitation: immunologic techniques, laboratory techniques; yeast two-hybrid screen: genetic techniques, laboratory techniques
IT Miscellaneous Descriptors
signal transduction
ORGN Classifier
Fungi 15000
Super Taxa
Plantae
Organism Name
yeast (common)
Taxa Notes
Fungi, Microorganisms, Nonvascular Plants, Plants
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common)
rat (common)
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 256376-24-6 (BAY41-2272)
86-01-1 (GTP)
7665-99-8 (cGMP)
7665-99-8 (cyclic GMP)
146724-94-9 (diethylamine diazeniumdiolate)
10102-43-9 (nitric oxide)
125978-95-2 (nitric-oxide synthase)
125978-95-2 (EC 1.14.13.39)
14402-89-2 (sodium nitroprusside)
9054-75-5 (soluble **guanylyl cyclase**)
9054-75-5 (**EC 4.6.1.2**)

L40 ANSWER 2 OF 3 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2003:498245 BIOSIS
DN PREV200300500329
TI A constitutively activated **mutant** of human soluble **guanylyl cyclase** (sGC): Implication for the mechanism of sGC activation.
AU **Martin, Emil**; Sharina, Iraida; Kots, Alexander; **Murad, Ferid** [Reprint Author]
CS Department of Integrative Biology and Pharmacology, Institute of Molecular Medicine, University of Texas Health Science Center, Houston, TX, 77030, USA
ferid.murad@uth.tmc.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (August 5 2003) Vol. 100, No. 16, pp. 9208-9213. print.
ISSN: 0027-8424 (ISSN print).
DT Article
LA English
ED Entered STN: 29 Oct 2003
Last Updated on STN: 29 Oct 2003
AB Heterodimeric alphabeta soluble **guanylyl cyclase** (sGC) is a recognized receptor for nitric oxide (NO) and mediates many of its

physiological functions. Although it has been clear that the heme moiety coordinated by His-105 of the beta subunit is crucial for mediating the activation of the enzyme by NO, it is not understood whether the heme moiety plays any role in the function of the enzyme in the absence of NO. Here we analyze the effects of biochemical and genetic removal of heme and its reconstitution on the activity of the enzyme. Detergent-induced loss of heme from the wild-type alphabeta enzyme resulted in several-fold activation of the enzyme. This activation was inhibited after hemin reconstitution. A heme-deficient **mutant** alphabetaCys-105 with Cys substituted for His-105 was constitutively active with specific activity approaching the activity of the wild-type enzyme activated by NO. However, reconstitution of **mutant** enzyme with heme and/or DTT treatment significantly inhibited the enzyme. **Mutant** enzyme reconstituted with ferrous heme was activated by NO and CO alone and showed additive effects between gaseous effectors and the allosteric activator 5-cyclopropyl-2-(1-(2-fluorobenzyl)-1H-pyrazolo(3,4-b)pyridin-3-yl)-pyrimidin-4-ylamine. We propose that the heme moiety through its coordination with His-105 the beta subunit acts as an endogenous inhibitor of sGC. Disruption of the heme-coordinating bond induced by binding of NO releases the restrictions imposed by this bond and allows the formation of an optimally organized catalytic center in the heterodimer.

CC Enzymes - General and comparative studies: coenzymes 10802
Physiology and biochemistry of bacteria 31000

IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics)

IT Chemicals & Biochemicals
soluble **guanylyl cyclase** [**EC 4.6.1.2**]: activation, alpha subunit, beta subunit, constitutively activated, **mutant** isoform

ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGN Classifier
Purple Nonsulfur Bacteria 08013
Super Taxa
Purple Bacteria; Anoxygenic Phototrophic Bacteria; Eubacteria; Bacteria; Microorganisms
Organism Name
Rhodospirillum rubrum (species)
Taxa Notes
Bacteria, Eubacteria, Microorganisms

RN **9054-75-5** (soluble **guanylyl cyclase**)
9054-75-5 (**EC 4.6.1.2**)

L40 ANSWER 3 OF 3 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
AN 2001:557076 BIOSIS
DN PREV200100557076
TI YC-1 activation of human soluble **guanylyl cyclase** has both heme-dependent and heme-independent components.
AU **Martin, Emil**; Lee, Yu-Chen; **Murad, Ferid** [Reprint author]
CS Department of Integrative Biology and Pharmacology, Institute of Molecular Medicine, University of Texas Health Science Center at Houston, Houston, TX, 77030, USA

ferid.murad@uth.tmc.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (Nobember 6, 2001) Vol. 98, No. 23, pp. 12938-12942. print. CODEN: PNASA6. ISSN: 0027-8424.
DT Article
LA English
ED Entered STN: 5 Dec 2001
Last Updated on STN: 25 Feb 2002
AB YC-1 (3-(5'-hydroxymethyl-2'furyl)-1-benzyl indazole) is an allosteric activator of soluble **guanylyl cyclase** (sGC). YC-1 increases the catalytic rate of the enzyme and sensitizes the enzyme toward its gaseous activators nitric oxide or carbon monoxide. In other studies the administration of YC-1 to experimental animals resulted in the inhibition of the platelet-rich thrombosis and a decrease of the mean arterial pressure, which correlated with increased cGMP levels. However, details of YC-1 interaction with sGC and enzyme activation are incomplete. Although evidence in the literature indicates that YC-1 activation of sGC is strictly heme-dependent, this report presents evidence for both heme-dependent and heme-independent activation of sGC by YC-1. The oxidation of the sGC heme by 1H-(1,2,4)oxadiazole(4,3-a)quinoxalin-1-one completely inhibited the response to NO, but only partially attenuated activation by YC-1. We also observed activation by YC-1 of a **mutant** sGC, which lacks heme. These findings indicate that YC-1 activation of sGC can occur independently of heme, but that activation is substantially increased when the heme moiety is present in the enzyme.
CC Enzymes - General and comparative studies: coenzymes 10802
Cardiovascular system - Blood vessel pathology 14508
IT Major Concepts
Enzymology (Biochemistry and Molecular Biophysics)
IT Diseases
thrombosis: vascular disease, platelet-rich
Thrombosis (MeSH)
IT Chemicals & Biochemicals
YC-1 [[3-(5'-hydroxymethyl-2'furyl)-1-benzyl indazole]: allosteric activator; soluble **guanylyl cyclase**: activation, heme-dependent, heme-independent
ORGN Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates
RN 154453-18-6Q (YC-1)
170632-47-0Q (YC-1)
154453-18-6Q ([3-(5'-hydroxymethyl-2'furyl)-1-benzyl indazole)
170632-47-0Q ([3-(5'-hydroxymethyl-2'furyl)-1-benzyl indazole)

=> => fil wpix
FILE 'WPIX' ENTERED AT 15:25:17 ON 13 JUL 2006
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FILE LAST UPDATED: 11 JUL 2006 <20060711/UP>
MOST RECENT DERWENT UPDATE: 200644 <200644/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:

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>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES, SEE
http://scientific.thomson.com/support/patents/coverage/latestupdates/

>>> PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf <<<

>>> FOR FURTHER DETAILS ON THE FORTHCOMING DERWENT WORLD PATENTS
INDEX ENHANCEMENTS PLEASE VISIT:
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<
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=> d all abeq tech abex

L76 ANSWER 1 OF 1 WPIX COPYRIGHT 2006 THE THOMSON CORP on STN
AN 2004-737505 [72] WPIX
DNC C2004-259351
TI Screening substance for heme independent inhibition of **soluble guanylyl cyclase sGC**, by assaying alphabetaCys105 **mutant sGC** enzyme for cGMP formation in presence of substance, and determining whether substance inhibits cGMP production.
DC B04 D16
IN MARTIN, E; MURAD, F
PA (TEXA) UNIV TEXAS SYSTEM
CYC 109
PI WO 2004087046 A2 20041014 (200472)* EN 39 A61K000-00
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
US 2004235079 A1 20041125 (200478) C12Q001-42
EP 1592787 A2 20051109 (200573) EN C12N009-12
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
ADT WO 2004087046 A2 WO 2004-US3853 20040211; US 2004235079 A1 Provisional US 2003-446427P 20030211, US 2004-777008 20040211; EP 1592787 A2 EP 2004-749320 20040211, WO 2004-US3853 20040211
FDT EP 1592787 A2 Based on WO 2004087046
PRAI US 2003-446427P 20030211; US 2004-777008 20040211
IC ICM A61K000-00; C12N009-12; C12Q001-42
ICS C12N015-09; C12Q001-48
AB WO2004087046 A UPAB: 20041109
NOVELTY - Screening a substance of interest for heme independent inhibition of **soluble guanylyl cyclase** (**sGC**), involves obtaining purified **alpha beta** (**Cys105**) **mutant sGC** enzyme/cell lysate containing **alpha beta** (**Cys105**) **mutant sGC** enzyme, assaying enzyme/cell lysate for formation of cGMP from GTP in presence/absence of substance, and comparing results, if present, to determine whether substance inhibits cGMP production by purified enzyme/cell lysate.
DETAILED DESCRIPTION - Screening (M1) a substance of interest for heme independent inhibition or activation of **soluble guanylyl cyclase** (**sGC**), involves obtaining

purified **alpha beta** (**Cys105**) **mutant** **sGC** enzyme or a cell lysate containing **alpha beta** (**Cys105**) **mutant** **sGC** enzyme, assaying the purified enzyme or cell lysate for formation of cGMP from GTP in the presence or absence of the substance, optionally, carrying out the assaying steps in the presence or absence of an activator other than the substance of interest, and comparing the results of formation of cGMP in the presence or absence of the substance and activator, if present, to determine whether the substance inhibits or enhances cGMP production by the purified enzyme or cell lysate.

INDEPENDENT CLAIMS are also included for:

(1) identifying (M2) a functional region of **sGC** that is responsible for **sGC** regulation, involves obtaining a library of deletion **mutants** of alpha subunit of **sGC**, producing **mutant** **sGC** enzymes containing beta (Cys105) subunit and alpha subunits with deletions obtained, obtaining cell lysates comprising the respective **mutant** **sGC** enzymes with alpha subunit deletions, optionally, purifying the **mutant** **sGC** enzymes, assaying and purified enzymes or cell lysates for formation of cGMP from GTP in the absence of activators or inhibitors, assaying purified wild-type **sGC** enzyme, or a cell lysate comprising the wild-type **sGC** enzyme, for formation of cGMP from GTP in the absence of activators or inhibitors, assaying purified **alpha beta** (**Cys105**) **mutant** **sGC** enzyme, or a cell lysate comprising the **alpha beta** (**Cys105**) **sGC** enzyme, for formation of cGMP from GTP in the absence of activators or inhibitors, comparing the results of the assaying steps to determine whether any the alpha subunit deletion decreases or increases the activity of the corresponding **mutant** enzyme tested in the step of assaying purified enzymes or cell lysates, as compared to the **alpha beta** (**Cys105**) **mutant** **sGC** enzyme in the step of assaying purified **alpha beta** (**Cys105**) **mutant**, to levels comparable or identical to that of the wild-type **sGC** enzyme, and identifying an alpha subunit deletion **mutant** from the library containing a deletion **mutation** that effects **sGC** activation using the results of the comparison;

(2) a method to aid in identifying structural features of **sGC** stimulation, involves crystallizing purified **alpha beta** (**Cys105**) **mutant** **sGC** enzyme in the presence or absence of dithiothreitol (DTT), comparing the resulting **sGC** enzyme crystals, and determining structural changes in the **sGC** protein associated with the presence or absence of DTT;

(3) increasing and/or sustaining intracellular production of cyclic GMP in a mammalian cell, involves providing **alpha beta** (**Cys105**) **mutant** **sGC**, or its beta (Cys105) subunit, to the cell, and/or constitutively expressing in the cell of the **alpha beta** (**Cys105**) **mutant** **sGC** gene, or its portion containing DNA encoding the beta (Cys105) subunit; and

(4) treating or preventing (M3) a mammalian pathophysiologic condition associated with cyclic GMP regulation of a cellular process, involves increasing and/or sustaining intracellular production of cGMP by constitutively expressing **alpha beta** (**Cys105**) **mutant** **sGC**, or inhibiting cGMP production by administering an inhibitor of **sGC** that acts independently of the heme moiety of **sGC**, in a mammal in need of such treatment or prevention.

ACTIVITY - Cardiant; Cardiovascular-Gen.; Thrombolytic; Antianginal; Hypotensive; Antiarteriosclerotic; Anticoagulant; Cytostatic;

Antibacterial; Immunosuppressive.
MECHANISM OF ACTION - Inhibitor of **sGC** (claimed). No supporting data is given.
USE - (M1) is useful for screening a substance of interest for heme independent inhibition or activation of **sGC**. (M3) is useful for treating or preventing a mammalian pathophysiologic condition associated with cGMP regulation of a cellular process, by treating or attenuating angina, treating a tumor or attenuating or preventing tumor metastasis, or treating or attenuating a penile dysfunction. The pathophysiologic condition comprises cardiovascular disease such as chronic heart disease, chronic hypertension, thrombosis, atherosclerosis, congestive heart failure, and myocardial infarction; post-angioplasty complication; complication arising from a vein graft operation; or septic shock (claimed).
ADVANTAGE - The **mutant sGC** enzyme obtained by (M1) does not require pharmacological activation and is constitutively active. The inhibitor of **sGC** acts independently of the heme moiety of **sGC** in a mammal.
DESCRIPTION OF DRAWING(S) - The figure shows a schematic representation of changes in the regulatory domain of wild-type and **alpha beta (Cys105) soluble guanylyl cyclase (sGC)**.
Dwg.8/8
FS CPI
FA AB; GI
MC CPI: B10-A07; B11-C08E; B11-C08E3; B11-C08G; B12-K04E; B14-A01; B14-D03; B14-F01; B14-F01D; B14-F02B; B14-F04; B14-F07; B14-G02; B14-H01; B14-N07; B14-S06; D05-H08; D05-H09; D05-H13
TECH UPTX: 20041109
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: In (M2), the alpha subunit deletion **mutant** is identified from the library of deletion **mutants** of alpha subunit of **sGC** that is critical for **sGC** activation. In (M3), the cGMP production is increased and/or sustained by delivering **alphabeta(Cys105) mutant sGC** enzyme or gene, or its beta(Cys105) subunit, to a cell in the mammal.
ABEX UPTX: 20041109
EXAMPLE - No relevant example is given.

=> => d his

(FILE 'HOME' ENTERED AT 14:48:03 ON 13 JUL 2006)
SET COST OFF

FILE 'HCAPLUS' ENTERED AT 14:48:15 ON 13 JUL 2006
L1 1 S US20040235079/PN OR (US2004-777008# OR WO2004-US03853 OR US20
E MARTIN E/AU
L2 995 S E3-E43
E MARTINEMIL/AU
E MARTIN EMIL/AU
L3 27 S E3,E4
E MURAD F/AU
L4 345 S E3-E6,E9
E FERID/AU
L5 31 S E4

FILE 'REGISTRY' ENTERED AT 14:51:15 ON 13 JUL 2006
E GYANYLYL CYCLASE/CN

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     FILE 'REGISTRY' ENTERED AT 14:51:23 ON 13 JUL 2006
                E GUANYLYL CYCLASE/CN
L6            1 S E3
L7          180 S GUANYLYL CYCLASE
L8            1 S L7 AND 105

     FILE 'HCAPLUS' ENTERED AT 14:53:10 ON 13 JUL 2006
L9         5429 S L6 OR L7
L10        8807 S (GUANYL OR GUANYLATE OR GUANYLYL)()CYCLASE
L11         118 S (EC OR "E C")()4 6 1 2
L12          26 S GUANYLCYCLASE OR GUANYLYLCYCLASE OR GUANYLATECYCLASE
L13        8903 S L9-L12
L14           8 S L13 AND ?CYS105?
L15           2 S L13 AND CYS 105
L16           3 S L13 AND (?ABCYS105? OR ?ABCYS 105 OR AB CYS 105 OR AB CYS105
L17           3 S L16 AND L14,L15

     FILE 'REGISTRY' ENTERED AT 14:58:07 ON 13 JUL 2006
                E CGMP/CN
L18           1 S E3
                E GTP/CN
L19           1 S E3

     FILE 'HCAPLUS' ENTERED AT 14:58:31 ON 13 JUL 2006
L20        3811 S L13 AND L18
L21         149 S L13 AND L19
L22       13879 S L18 AND (GTP OR CGMP OR C GMP)
L23           3 S L20-L22 AND L14-L17
L24           1 S L17 NOT L23
L25           3 S L17,L24 AND L1-L5,L9-L17,L20-L24
L26         164 S L1-L5 AND L13
L27           5 S L26 AND MUTANT
L28           2 S L27 NOT L25
L29           5 S L25,L27,L28

     FILE 'BIOSIS' ENTERED AT 15:02:50 ON 13 JUL 2006
                E MURAD/AU
                E MURAD F/AU
L30         624 S E3-E6,E8
                E FERID/AU
                E MARTIN E/AU
L31        1486 S E3-E37
                E MARTIN EMIL/AU
L32          19 S E3
L33        2109 S L30-L32
L34       10650 S L13
L35         227 S L33 AND L34
L36           3 S L35 AND MUTANT
L37           0 S L35 AND MUTAT?
L38           0 S L35 AND (?CYS105? OR CYS 105)
L39           0 S L35 AND (?ABCYS105? OR ?ABCYS 105 OR AB CYS 105 OR AB CYS105
L40           3 S L36 AND L30-L39

     FILE 'MEDLINE' ENTERED AT 15:06:02 ON 13 JUL 2006
L41        9256 S L13
L42          14 S L41 AND (?CYS105? OR CYS 105)
L43           0 S L41 AND (?ABCYS105? OR ?ABCYS 105 OR AB CYS 105 OR AB CYS105
L44          13 S L42 AND PY<=2003
L45         619 S L41 AND SGC
L46        3071 S L41 AND SOLUB?
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L47           3 S L45,L46 AND L42
L48           1 S L42 AND L45
L49         430 S L41 AND (MUTANT? OR MUTAT?)
L50           1 S L49 AND L42
L51          27 S L49 AND L45
L52          84 S L49 AND L46
L53          84 S L50-L52
L54          64 S L53 AND PY<=2003
                E MUTATION/CT
                E E3+ALL
L55         229 S E4+NT AND L41
L56          36 S E51+NT AND L41
L57           6 S E52+NT AND L41
L58           0 S E53+NT AND L41
                E MUTANT/CT
                E E5+ALL
L59           3 S E4+NT AND L41
L60           1 S L55-L59 AND L42

     FILE 'HCAPLUS' ENTERED AT 15:11:51 ON 13 JUL 2006
                SEL HIT RN L29

     FILE 'REGISTRY' ENTERED AT 15:12:18 ON 13 JUL 2006
L61           3 S E1-E3
L62           3 S L61 AND L6-L8,L18,L19

     FILE 'MEDLINE' ENTERED AT 15:12:51 ON 13 JUL 2006

     FILE 'BIOSIS' ENTERED AT 15:13:12 ON 13 JUL 2006

     FILE 'WPIX' ENTERED AT 15:13:31 ON 13 JUL 2006
L63         307 S L10 OR L11 OR L12
                E GUANYL/CN
L64           1 S E4,E7,E8,E11
L65          25 S RA1GJA/DCN OR 269548-0-0-0/DCRE OR L64/DCR
L66         309 S L63,L65
L67           1 S L66 AND (?CYS105? OR CYS 105)
L68           1 S L66 AND (?ABCYS105? OR ?ABCYS 105 OR AB CYS 105 OR AB CYS105
L69           1 S L66 AND ALPHABETA()(CYS105 OR CYS 105)
L70           1 S L68-L69
L71          10 S L66 AND MUTANT?
L72          14 S L66 AND MUTAT?
L73          28 S L66 AND (SGC OR S GC OR SOLUB? GC)
L74         103 S L66 AND SOLUB?()L63
L75           4 S L71,L72 AND L73,L74
L76           1 S L70 AND L75

     FILE 'WPIX' ENTERED AT 15:25:17 ON 13 JUL 2006
L77           4 S L66 AND (MARTIN E? OR MURAD F? OR FERID ?)/AU
L78           3 S L77 NOT L76

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